

LASIC et al.

Serial No.: 09/771,151

Filed: January 26, 2001

For: LIPOSOMES CONTAINING AN ENTRAPPED COMPOUND IN SUPERSATURATED SOLUTION

17. **(Amended)** The composition of claim 11, wherein selection of a liposome size comprises [includes] a liposome size effective to inhibit formation of precipitated drug in an internal liposome compartment.

18. The composition of claim 14, wherein the hydrophilic polymer chain is polyethylene glycol.

Remarks

Claims 2 and 10 have been cancelled. Claims 1, 3-9, 14-15, and 17 have been amended. Thus, claims 1, 3-9, and 11-18 are pending in the above-identified patent application. The claims have been amended to more clearly define Applicants' invention.

In amending the above claims, Applicants are not acquiescing to objections or rejections asserted by the Examiner. Applicants have amended the claims to further the prosecution of this application and retain the right to file divisional or continuing applications to claim any canceled subject matter.

No new matter has been added by these amendments. Reconsideration and withdrawal of the rejections in light of the preceding amendments and following remarks are respectfully requested.

Extension of Time

A petition for a three-month extension of time and the fee therefore accompanies this response.

The Rejection Under 35 U.S.C. §112 Second Paragraph

Claims 1-18 were rejected under 35 U.S.C. §112 second paragraph as allegedly indefinite. The Examiner has alleged several issues which are deemed to be indefinite including: (1) how a supersaturated solution of a compound is entrapped in liposomes; (2) with respect to the term

LASIC et al.

Serial No.: 09/771,151

Filed: January 26, 2001

For: LIPOSOMES CONTAINING AN ENTRAPPED COMPOUND IN SUPERSATURATED SOLUTION

“condition,” what the condition is and where the condition occurs; (3) what is conveyed by the phrase capable of exhibiting at least a two-fold increase in response to a condition; (4) how is liposome size selected; (5) a suggestion to use the term comprises and not the term “includes” in the claims; (6) a clarification vis-à-vis claim 10; (7) the recitation of claim 11 has led the Examiner to ask if the compound of claim 11 is not in a super saturated solution after entrapment; (8) claims 10 and 14-15 appear to recite a composition when the claims are directed to a method; (9) a clarification vis-à-vis 16. To the extent the rejection applies to claims 1-18 as amended, it is respectfully traversed.

Claims have been amended according to several of the Examiners suggestions. As to the remaining above-outlined issues, Applicant's Representative believe the terms and phrases employed in the claims are definite in view of the claims, the specification, and as would be understood by one of skill in the art. For example, at page 6, lines 24-30, with respect to the Examiner's concerns vis-à-vis supersaturation and conditions employed to achieve this, compounds useful in the invention are those that typically have a limited solubility in water at room temperature, but undergo a substantial increase in solubility with an increase in temperature. This achieves at least a two-fold, a three-fold, and even a four fold increase in room temperature aqueous solubility. This result can be realized several ways, such as by increasing solvent temperature, by addition of a co-solvent, or by changing solvent pH. A specific example of a compound (cisplatin) in a supersaturated state is described in Example 1 in the specification. Further conditions have been specifically recited in claim 1 as amended.

As to liposome size, at page 8, lines 14, and 19-20, Applicants specifically state that liposomes are size selected to inhibit the formation of precipitated drug. Liposome size may range from about 60nm to about 1000nm.

In short, it is well recognized that a claim that is understandable to one of skill in the art and defines the subject matter that Applicant(s) regards as the invention meets the requirements of 35 U.S.C. §112, second paragraph. All that is required by the second paragraph of section 112, is that the claims set out and circumscribe a particular area that the Applicant(s) regards as

LASIC et al.

Serial No.: 09/771,151

Filed: January 26, 2001

For: LIPOSOMES CONTAINING AN ENTRAPPED COMPOUND IN SUPERSATURATED SOLUTION

the invention with a reasonable degree of precision and particularity. Applicants have readily defined this particular area such that one of skill in the art would understand all of the claim language when read in light of the specification and it is as precise as the subject matter requires.

Withdrawal and reconsideration of the rejections under 35 U.S.C. §112, second paragraph are respectfully requested.

The Rejections Under 35 U.S.C. §102(b)

To anticipate a claim, the cited document must contain all the elements of the claims, and the document must enable one skilled in the art to carry out the invention.

1. Claims 1-6, 10-13, and 15-17 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by EP 0177 223. This rejection is respectfully traversed.

EP 0177 223 relates to a pharmaceutical multi-phase composition for use as a drug delivery system. The system is described as a “multi-component” system (page 7, lines 6-9). This includes, for example, an active ingredient that is present in “two” states in the invention, i.e., in solution and in solid form within and outside the lipid vesicles (page 7, lines 9-11). Advantages of this multi-component system are detailed at page 9 beginning at line 31. EP 0177 223 fails to describe a compound having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition wherein the condition may be (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) changing solvent pH.

As EP 0177 223 fails to disclose all the elements of claims 1-6, 11-13, and 15-17, the document fails to anticipate Applicants invention.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) are respectfully requested.

2. Claims 1-6, 8-13, and 15-17 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by EP 0551 169. This rejection is respectfully traversed.

LASIC et al.

Serial No.: 09/771,151

Filed: January 26, 2001

For: LIPOSOMES CONTAINING AN ENTRAPPED COMPOUND IN SUPERSATURATED SOLUTION

EP 0551 169 relates to a liposome composition, in which a water-soluble drug is encapsulated in high concentration within liposomes, and a process for its production (column 1, lines 3-6). The inventors have found that when a drug in liposomes is present in the supersaturated state or in the form of solids or crystals, the amount of the drug per unit lipid amount can be increased (column 2, lines 20-24). In contrast, Applicants invention specifically employs liposomes that inhibit formation of precipitated drug, and employs compounds having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition wherein the condition may be (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) .

As EP 0551 169 fails to disclose all the elements of claims 1-6, 8-9, 11-13, and 15-17, the document fails to anticipate Applicants invention.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) are respectfully requested.

3. Claims 1-18 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 98/07409. This rejection is respectfully traversed.

WO 98/07409 relates to a liposomal composition containing an entrapped cisplatin compound (page 1, lines 6-7). The drug is entrapped in the inner aqueous compartment in dissolved or in precipitated form (page 4, lines 34-35). In contrast, Applicants invention specifically employs liposomes that inhibit formation of precipitated drug, and employs compounds having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition wherein the condition may be (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii).

As WO 98/07409 fails to disclose all the elements of claims 1-9 and 11-18, the document fails to anticipate Applicants invention.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b) are respectfully requested.

LASIC et al.

Serial No.: 09/771,151

Filed: January 26, 2001

For: LIPOSOMES CONTAINING AN ENTRAPPED COMPOUND IN SUPERSATURATED SOLUTION

The Rejection Under 35 U.S.C. §103(a)

Claims 7, 14 and 18 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over either EP 0177 223 or EP 0551 169 in combination with Woodle et al., (U.S. Patent No: 5,013,556). This rejection, as it applies to the claims as amended, is respectfully traversed.

Applicants respectfully traverse this rejection for a number of reasons. Establishment of a *prima facie* case of obviousness requires that the cited documents teach or suggest all of the limitations of the rejected claims. In addition, some suggestion or motivation must be provided to modify the documents to reach the claimed invention. Further, a document must be considered as a whole, including those portions of the document that teach away from the claimed invention.

As discussed above, Applicants respectfully submit that all of elements recited in claims 7, 14, and 18 are not taught or suggested by either EP 0177 223 or EP 0551 169. Moreover, the secondary document (Woodle et al.) fails to supply that which is lacking from EP 0177 223 or EP 0551 169. Although Woodle et al. mention the use of a hydrophilic polymer, this does not overcome the deficiencies of the primary documents.

In short, the cited documents, either alone or in combination, fail to teach, suggest, or motivate one of skill in the art to provide methods and compositions as claimed by Applicants. For the above reasons, Applicants respectfully submit that the invention recited in claims 7, 14, and 18 are patentable over either EP 0177 223 or EP 0551 169 in combination with Woodle et al., (U.S. Patent No: 5,013,556). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) are respectfully requested.

LASIC et al.

Serial No.: 09/771,151

Filed: January 26, 2001

For: LIPOSOMES CONTAINING AN ENTRAPPED COMPOUND IN SUPERSATURATED SOLUTION

Conclusion

In light of the remarks presented herein, it is respectfully submitted that pending claims 1, 3-9, and 11-18 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representative at the below-listed telephone number if it is believed that prosecution of this application may be assisted thereby.

CERTIFICATE UNDER 37 C.F.R. 1.8:

The undersigned hereby certifies that this paper is being deposited in the United States Postal Service, as first class mail, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on this 30th day of Sept., 2002.

Katrina M. Ghafghaichi
Katrina Ghafghaichi

30 SEPT 2002

Date

Respectfully Submitted,

ALZA Corporation
1900 Charleston Road
Mountain View, CA 94043
(650) 564-5000

By:

Paul B. Simboli

Paul B. Simboli

Reg. No. 38,616

Direct Dial: (650) 564-7840



- Sub
B1
- a1
1. **(Amended)** A method for preparing liposomes comprising:
- selecting a compound having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition selected from the group consisting of: (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) changing solvent pH;
 - selecting liposomes of a size effective to inhibit precipitation of the compound when entrapped in a liposome; and
 - entrapping the compound in the liposomes in a supersaturated state.

3. **(Amended)** The method of claim 1, wherein selecting the liposomes comprises selecting liposomes that have a liposome size of between about 60 nm to about 1000 nm.

4. **(Amended)** The method of claim 1, wherein selecting the liposomes comprises preparing liposomes having an entrapped compound at liposome size intervals between about 60 to about 1000 nm and analyzing the liposomes for the presence or absence of a precipitated compound.

a2

5. **(Amended)** The method of claim 1, wherein selecting the liposomes comprises preparing liposomes having an entrapped compound at liposome size intervals between about 60 nm to about 1000 nm and analyzing the liposomes for the presence or absence of a precipitated compound.

6. **(Amended)** The method of claim 1, wherein the entrapping comprises preparing a solution of lipids.

7. **(Amended)** The method of claim 6, wherein the preparing comprises preparing a solution of lipids that comprises a lipid derivatized with a hydrophilic polymer.

a2
concl

8. **(Amended)** The method of claim 6, wherein the preparing comprises a solution of lipids effective to form a rigid lipid bilayer.

9. **(Amended)** The method of claim 1, further comprises removing from an external liposome suspension medium the condition selected to maintain the drug above the room temperature solubility limit.

11. A liposome composition comprising:

a suspension of liposomes composed of a vesicle-forming lipid, and

a compound entrapped in the liposomes, wherein the compound prior to entrapment is maintained in the liposomes in a supersaturated state.

12. The composition of claim 11, wherein the compound exhibits a two-fold increase in aqueous solubility in response to a condition selected from the group consisting of: (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) changing solvent pH.

13. The composition of claim 11, wherein the liposomes have a liposome size of between about 60 nm to about 1000 nm.

a3

14. **(Amended)** The composition of claim 11, wherein the liposomes further comprise a lipid derivatized with a hydrophilic polymer chain.

15. **(Amended)** The composition of claim 11, wherein the liposomes comprise saturated vesicle-forming phospholipids.

16. A method for preparing liposomes comprising:

preparing an aqueous concentrated solution of a compound suitable for entrapment in an internal aqueous compartment of the liposomes;

hydrating a lipid film or lipid solution with a concentrated solution of the compound to form liposomes; and

sizing the liposomes to a size effective to inhibit formation of precipitated compound, thereby maintaining the entrapped compound in a supersaturated state.

Q4

17. **(Amended)** The composition of claim 11, wherein selection of a liposome size comprises a liposome size effective to inhibit formation of precipitated drug in an internal liposome compartment.

18. The composition of claim 14, wherein the hydrophilic polymer chain is polyethylene glycol.



1. **(Amended)** A method for preparing liposomes comprising:
selecting a compound having room temperature water solubility capable of exhibiting at least a two-fold increase in response to a condition selected from the group consisting of: (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) changing solvent pH;
selecting liposomes of a size effective to inhibit precipitation of the compound when entrapped in a liposome; and
entrapping the compound in the liposomes in a supersaturated state.
3. **(Amended)** The method of claim 1, wherein selecting the liposomes comprises [includes] selecting liposomes that have a liposome size of between about 60 nm to about 1000 nm.
4. **(Amended)** The method of claim 1, wherein selecting the liposomes comprises [includes] preparing liposomes having an entrapped compound at liposome size intervals between about 60 to about 1000 nm and analyzing the liposomes for the presence or absence of a precipitated compound.
5. **(Amended)** The method of claim 1, wherein selecting the liposomes comprises [includes] preparing liposomes having an entrapped compound at liposome size intervals between about 60 nm to about 1000 nm and analyzing the liposomes for the presence or absence of a precipitated compound.
6. **(Amended)** The method of claim 1, wherein the entrapping comprises [includes] preparing a solution of lipids.

7. **(Amended)** The method of claim 6, wherein the preparing comprises [includes] preparing a solution of lipids that comprises [include] a lipid derivatized with a hydrophilic polymer.
8. **(Amended)** The method of claim 6, wherein the preparing comprises [includes preparing] a solution of lipids effective to form a rigid lipid bilayer.
9. **(Amended)** The method of claim 1, further comprises [including] removing from an external liposome suspension medium the condition selected to maintain the drug above the room temperature solubility limit.
11. A liposome composition comprising:
a suspension of liposomes composed of a vesicle-forming lipid, and
a compound entrapped in the liposomes, wherein the compound prior to entrapment is maintained in the liposomes in a supersaturated state.
12. The composition of claim 11, wherein the compound exhibits a two-fold increase in aqueous solubility in response to a condition selected from the group consisting of: (i) increasing solvent temperature, (ii) adding a co-solvent, and (iii) changing solvent pH.
13. The composition of claim 11, wherein the liposomes have a liposome size of between about 60 nm to about 1000 nm.
14. **(Amended)** The composition of claim 11 [1], wherein the liposomes further comprise a lipid derivatized with a hydrophilic polymer chain.
15. **(Amended)** The composition of claim 11 [1], wherein the liposomes comprise saturated vesicle-forming phospholipids.
16. A method for preparing liposomes comprising:

preparing an aqueous concentrated solution of a compound suitable for entrapment in an internal aqueous compartment of the liposomes; hydrating a lipid film or lipid solution with a concentrated solution of the compound to form liposomes; and sizing the liposomes to a size effective to inhibit formation of precipitated compound, thereby maintaining the entrapped compound in a supersaturated state.

17. **(Amended)** The composition of claim 11, wherein selection of a liposome size comprises [includes] a liposome size effective to inhibit formation of precipitated drug in an internal liposome compartment.

18. The composition of claim 14, wherein the hydrophilic polymer chain is polyethylene glycol.